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Vitamin C for preventing and treating tetanus (Review)

Hemilä H, Koivula T



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Vitamin C for preventing and treating tetanus

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ABSTRACT

Background

Tetanus is a severe disease that can be prevented by vaccination. In developing countries vaccination coverage is not always high. Cases still occur also in developed countries, particularly in elderly people owing to their reduced immuno protection. There are about 1 million tetanus cases per year globally. In animal studies, vitamin C has protected against various infections and bacterial toxins. In a study with rats, vitamin C protected against the purified tetanus toxin.

Objectives

To assess the prophylactic and therapeutic effect of vitamin C on tetanus.

Search methods

In May 2013 we searched the Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); and Ovid EMBASE for this third update.

Selection criteria

Controlled trials of vitamin C as a prevention or treatment for tetanus, whether or not these were placebo controlled, in any language, published or unpublished. Two review authors independently made inclusion decisions.

Data collection and analysis

Both review authors independently extracted data from trial reports and assessed methodological quality. Since one of the cells in a 2×2 table had no events, we calculated the odds ratio (OR) and its 95% confidence interval (CI) for case fatality rate by using the Peto-method. Another of the 2×2 tables had no empty cells and the inverse-variance method was used to calculate its risk ratio (RR) estimate and 95% CI. We also used the Fisher's exact test to calculate the exact 95% CI for the OR of the 2×2 table with the empty cell.

Main results

One single trial was eligible for inclusion. This non-randomised, unblinded, controlled trial undertaken in Bangladesh involved 117 tetanus patients. Vitamin C at a dosage of 1 g/day was administered intravenously alongside conventional treatment. At recruitment, the participants were stratified into two age groups and the results were reported by age. There was a significant difference in the vitamin C effect between the two age groups ($P = 0.01$). In the tetanus patients aged 1 to 12 years ($n = 62$), vitamin C treatment was

associated with a 100% reduction in case fatality rate (95% CI from -100% to -94%). In patients aged 13 to 30 years (n = 55), vitamin C treatment was associated with a 45% reduction in case fatality rate (95% CI from -69% to -5%).

Authors' conclusions

A single, non-randomised, poorly reported trial of vitamin C as a treatment for tetanus suggests a considerable reduction in mortality. However, concerns about trial quality mean that this result must be interpreted with caution and vitamin C cannot be recommended as a treatment for tetanus on the basis of this evidence. New trials should be carried out to examine the effect of vitamin C on tetanus treatment.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating tetanus

Tetanus is a disease caused by tetanus toxin, which is produced by the bacterium *Clostridium tetani*. This bacterium typically infects penetrating wounds contaminated by foreign material such as soil. In developing countries, poor hygiene after childbirth may cause tetanus in newborn babies. Even though vaccination has dramatically decreased the burden of tetanus, there are still about 1 million tetanus cases per year globally. We found one controlled trial that examined whether one gram per day of intravenous vitamin C would help in the treatment of tetanus patients. Vitamin C was used alongside standard treatments for tetanus. Intravenous vitamin C reduced the mortality of children aged between 1 and 12 with tetanus by 100% and that of 13 to 30 year old patients by 45%. The trial was not properly conducted and caution is required in the interpretation of the findings. Vitamin C cannot be recommended as a treatment for tetanus on the basis of this single study. Further investigation of the role of vitamin C in tetanus treatment is warranted.

BACKGROUND

Description of the condition

'Tetanus' denotes a disease caused by tetanus toxin (tetanospasmin), a protein that is produced by the anaerobic bacterium *Clostridium tetani*. Although the pathological definition of tetanus is based on the specified bacterium and its toxin, the diagnosis is made clinically. The clinical picture is dominated by muscle spasms and rigidity. Often the first sign is rigidity of the jaw muscles, followed by stiffness of the neck, difficulty in swallowing, and rigidity of the abdominal muscles. Other symptoms include elevated temperature, raised blood pressure, and an episodically rapid heart rate. Tetanus may lead to complications such as fractures of the spine or long bones because of contractions and convulsions, and to pulmonary embolism, bed sores and nosocomial infections due to prolonged hospitalisation. The current treatment of tetanus consists, for example, of surgical debridement of the wound and antibiotic therapy (metronidazole) to remove the source of infection, tetanus immune globulin to neutralize circulating toxin, and benzodiazepine for sedation and muscle relaxation (Thwaites 2006; Gibson 2009; Reddy 2010; Afshar 2011; Ataro 2011; CDC 2013; WHO 2013).

Tetanus is typically caused by anaerobic bacterial growth in a contaminated penetrating wound. Vaccination against tetanus has dramatically reduced the incidence of the disease in developed countries, but infrequent cases occur, particularly in elderly people owing to reduced immuno protection (Gergen 1995; Yuan 1997). Nevertheless, about 1 million cases of tetanus are reported worldwide annually (Afshar 2011). In developing countries case fatality rate is about 50%, whereas in developed countries with intensive care units (ICU) the case fatality rate is less than 20% (Afshar 2011).

In developing countries, neonatal tetanus causes over 100,000 infant deaths per year, due largely to poor umbilical hygiene after childbirth. According to the World Health Organization (WHO), Somalia had the highest rate in 1999, with 16.5 neonatal tetanus deaths per 1000 live births (WHO 2000). It is noteworthy that vitamin C deficiency has also been particularly common in Somalia (WHO 1999). Vaccination of mothers would prevent the majority of these cases and the WHO has campaigned to increase the coverage of vaccination in developing countries (WHO 2000; Demicheli 2013; Khan 2013; WHO 2013).

Although the molecular mechanisms of the tetanus toxin in the initiation of pathogenesis are well known, the later stages of the pathological cascade are inadequately understood. There is evi-

dence indicating that disturbances in autonomic control with sympathetic overactivity (e.g. elevated blood pressure, rapid heart rate) could play a crucial role in the pathophysiology of severe tetanus cases (Daher 1997; Wasay 2005; CDC 2013). The possible role of catecholamines (stress hormones) in tetanus was supported by data reported by Thwaites 2006a. The concentrations of epinephrine and norepinephrine were much higher in tetanus patients than in other critically ill patients and, amongst the tetanus patients, the concentrations were higher in those who had more severe forms of tetanus.

Description of the intervention

Vitamin C was identified in the early 1900s in the search for the substance, the deficiency of which causes scurvy (Carpenter 1986). After the identification there was interest in its effects on diseases unrelated to scurvy, but the role of vitamin C on other diseases is still unsettled.

According to systematic reviews, over two dozen controlled trials have shown that vitamin C shortens the duration of colds (Hemilä 2013), five trials found that vitamin C halved the incidence of colds in participants who endured short-term heavy acute physical stress (Hemilä 2013), three trials found that vitamin C alleviated exercise-induced bronchoconstriction (Hemilä 2013a), two trials reported therapeutic benefit for pneumonia patients and three reported prophylactic benefit against pneumonia under special circumstances (Hemilä 2013b). In randomised trials with critically ill patients, vitamin C alone (Tanaka 2000; Papoulidis 2011; Bjorndahl 2012) or in the combination with vitamin E (Nathens 2002) significantly decreased the length of mechanical ventilation or the length of ICU stay or both. Although such findings indicate that the effects of vitamin C are not limited to preventing scurvy, their practical significance is not yet clear.

Two large trials with US male physicians and female health professionals found no benefits of 0.5 g/day of vitamin C (Cook 2007; Sesso 2008), but these trials are not discordant with the possibility that vitamin C administration may influence health on special conditions, such as when a person endures heavy physical activity or suffers from an infection.

An early case report claimed benefit of vitamin C against tetanus in an unvaccinated six-year-old boy in the USA, but the specific role of vitamin C cannot be inferred from the report (Klenner 1954).

Usually vitamin C is administered as tablets, but it can also be administered intravenously. A pharmacokinetic study compared oral and intravenous administration and found substantially higher plasma levels when vitamin C was administered by intravenous route compared with oral administration (Padayatty 2004). The highest dose used in the pharmacokinetic study, 100 g of vitamin C intravenously given over a few hours, increased the plasma concentration peak to 15,000 $\mu\text{mol/L}$, which is over 100 times

the plateau level reached by high dose oral administration (Levine 1996; Padayatty 2004).

Vitamin C is safe in high doses. A dose of approximately 10 mg/day prevents scurvy but, according to the US nutritional recommendations, the 'tolerable upper intake level' is 2 g/day for adults (IOM 2000). The basis for this upper limit is the appearance of diarrhoea, which is, however, a trivial adverse effect that disappears quickly with a reduction in intake. Several other reviewers have also concluded that vitamin C is safe in doses ranging to several grams per day (Hathcock 2005; Hemilä 2006).

How the intervention might work

As described above, elevated levels of catecholamines (stress hormones) may play a role in the pathophysiology of tetanus. Vitamin C might influence tetanus, for example, through its effects on catecholamine metabolism. First, vitamin C is involved in the synthesis of norepinephrine and the adrenal glands have the highest concentration of this vitamin in the body (Diliberto 1991; Rice 2000; Patak 2004; Kato 2006). Second, in an animal model vitamin C with vitamin E and β -carotene protected against the cardiotoxic effects of high levels of norepinephrine (Qin 2001). Third, various infections and purified bacterial toxins deplete vitamin C from the adrenal glands and other tissues (Hemilä 2006). Thus, vitamin C might influence conditions where catecholamine metabolism is changed.

A few laboratory studies have shown that vitamin C improved the functions of phagocytes and the proliferation of T-lymphocytes, indicating that it has roles in the immune system (Hemilä 2006; Webb 2007). In dozens of animal studies, vitamin C increased resistance against diverse infections and purified bacterial toxins (Hemilä 2006). In particular, Dey 1966 reported that five rats administered twice the minimal lethal dose of tetanus toxin all died, whereas 25 rats administered vitamin C either before or after the toxin all lived (Hemilä 2006). Vitamin C also reduced mortality in mice caused by toxins of several *Clostridium* species (Büller Souto 1939 [see the data extracted in: Clemetson 2002; Hemilä 2006]).

Chakrabarti 1955 reported that tetanus patients had lower plasma vitamin C levels than healthy people, and tetanus patients who died had lower levels than those who survived. Furthermore, tetanus patients had elevated levels of dehydroascorbate, which is the oxidized form of vitamin C. Such changes in vitamin C metabolism provide a further rationale to test vitamin C for tetanus patients.

Although vitamin C influences the immune system, it may be important only in particular conditions. For example, it is possible that variation in dietary vitamin C intake is not crucial in the ordinary western population because of their relatively high dietary intake levels, yet vitamin C might be a limiting factor in populations with low intakes. In the extreme, the prevalence of scurvy

(vitamin C deficiency) was reported to be up to 44% in refugee camps in Somalia ([WHO 1999](#)).

Why it is important to do this review

Tetanus is a severe disease afflicting about 1 million people annually and vitamin C is a safe and inexpensive essential nutrient. The possibility that vitamin C may have an action on tetanus is therefore worthy of systematic consideration.

Links to the publications cited in this Background section, for which full text versions are available, can be found at: www.mv.helsinki.fi/home/hemila/CT

OBJECTIVES

To determine the effects of vitamin C supplementation for:

- (1) preventing the development of tetanus in vaccinated and unvaccinated individuals;
- (2) treating patients with a diagnosis of tetanus.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled clinical trials, both randomised and non-randomised. The review includes studies with and without placebo control since, firstly, it is unlikely that being aware of taking or not taking vitamin C would influence such a severe disease as tetanus; and secondly, a recent meta-analysis of trials comparing a placebo group with a no-treatment group found no evidence of a substantial placebo effect on binary outcomes, although placebo did have an effect on pain measured as a continuous outcome ([Hrobjartsson 2010](#)).

Types of participants

We included studies involving people of any age and sex, either vaccinated or unvaccinated (prevention) or who had a diagnosed condition of tetanus (treatment). In this review we include both neonatal tetanus and tetanus cases occurring after the neonatal period.

Types of interventions

Studies in which treatment with vitamin C was the only systematic difference between the treatment arms were eligible for inclusion. We included studies comparing outcomes after the administration of vitamin C (ascorbic acid or its salts or other derivatives; orally or intravenously) with the administration of no or a lower dose of vitamin C. We did not apply restrictions on the dosage and frequency of administration of vitamin C, and we considered treatment trials using a single dose and trials in which vitamin C was administered with other treatments, provided co-interventions did not differ between the treatment arms. We regarded 'prevention trials' as those in which regular vitamin C was administered to people who did not have tetanus and 'treatment trials' as those in which vitamin C was administered after the diagnosis of tetanus.

Types of outcome measures

We applied any definition of tetanus applied by the original study authors.

Primary outcomes

Prevention trials:

1. Incidence of tetanus.

Treatment trials:

1. Mortality;
2. Duration of hospital stay.

Secondary outcomes

Prevention trials:

1. Mortality;
2. Duration of hospital stay;
3. Severity of symptoms and complications.

Treatment trials:

1. Severity and occurrence of complications such as fractures and nosocomial infections.

Search methods for identification of studies

Electronic searches

For an outline of the search methods used in second update of this review see [Appendix 1](#).

We searched the following databases in May 2013 for this third update:

- The Cochrane Wounds Group Specialised Register (searched 22 May 2013);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 4);
- Ovid MEDLINE (1946 to May Week 2 2013);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, May 16, 2013);
- Ovid EMBASE (2011 to 2013 Week 19);

The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):

#1 MeSH descriptor Tetanus explode all trees

#2 tetanus

#3 (#1 OR #2)

#4 MeSH descriptor Ascorbic Acid explode all trees

#5 ascorb* or "vitamin C"

#6 (#4 OR #5)

#7 (#3 AND #6)

The search strategies for Ovid MEDLINE and Ovid EMBASE can be found in [Appendix 2](#) and [Appendix 3](#) respectively. No methodological filters were used. No date or language restrictions were applied.

Searching other resources

Previously, [Briggs 1984](#) carried out extensive literature searches and published a bibliography containing over 400 references to papers related to vitamin C and infections, which we checked, as well as the reference lists of two books on potential clinical effects of vitamin C ([Stone 1972](#); [Levy 2002](#)). We also searched the reference lists of all other pertinent reviews and of the potentially eligible studies identified in our search.

Data collection and analysis

Selection of studies

The first review author searched the literature and both review authors independently assessed the titles and abstracts to identify potentially relevant articles. We obtained full versions of all potentially eligible articles, which we scrutinised independently.

Data extraction and management

Both review authors independently extracted pertinent data from the articles selected. We recorded the following quality features

of the trials on data extraction forms as 'yes', 'no', 'unclear': randomised allocation, allocation concealment, blinding of participants, blinding of investigator, blinding of outcome assessor, blind data analysis and intention-to-treat analysis. We also recorded baseline measurements and percentage dropout during follow up.

Assessment of risk of bias in included studies

We did not calculate any quality scores because "the use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews" ([Higgins 2011](#)). We describe the weaknesses and strengths of the included trial explicitly in the '[Risk of bias in included studies](#)' section.

Measures of treatment effect

We entered the case fatality rate data of the identified [Jahan 1984](#) study to the [RevMan 2012](#) computer program and calculated the odds ratio (OR) as an approximation of the risk ratio (RR) ([Rothman 1998](#)), presenting the results with the 95% confidence intervals (CI). Because one cell in the 2×2 table was empty in the comparison of children we used the Peto-method for calculating the OR. We also used the Fisher's exact test of the [R-Project 2013](#) package to calculate the exact 95% CI for the OR and the Fisher's exact test P-value for the comparison. We used two-tailed P values in this review.

Unit of analysis issues

The patients in the [Jahan 1984](#) trial were divided into two wards by vitamin C administration. Although this may cause bias in treatment and observations, it does not affect the unit of analysis (the individual patient), because tetanus is not a contagious disease.

Assessment of heterogeneity

We assessed the heterogeneity of comparisons by using I^2 ([Higgins 2003](#)). This examines the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 greater than about 70% indicates a high level of heterogeneity. We also used the χ^2 test to calculate the probability that the observed heterogeneity was caused by chance.

Data synthesis

We did not pool the age groups of the [Jahan 1984](#) trial, because there was a high level of heterogeneity.

RESULTS

Description of studies

No new eligible trials were identified in the searches carried out for the 2013 update of this review. From the original search we found one eligible controlled trial that provided data pertinent to vitamin C in the treatment of tetanus patients (Jahan 1984), but we found no trials reporting on the prevention of tetanus with vitamin C. The main features of the Jahan trial are briefly summarised in the table 'Characteristics of included studies', but described in detail in the following section because its weaknesses and strengths are crucial when considering the validity of its findings. The Jahan 1984 trial was carried out in Bangladesh in the early 1980s. A total of 117 tetanus patients were admitted to the Infectious Disease Hospital in Dhaka and divided into two age groups at recruitment. There were 62 children in the age group 1 to 12 years, and 55 children and adults in the age group 13 to 30 years. The Jahan report is available at www.mv.helsinki.fi/home/hemila/CT

Risk of bias in included studies

Jahan 1984 did not describe the allocation method, but the vitamin C and control arms were of the same size: 31 vitamin C patients compared with 31 control participants in the younger age band; and 27 (vitamin C) compared with 28 (control) in the older participants. Allocation concealment could not be judged from the report. Patients allocated to the vitamin C group received 1 g/day intravenously "in addition to conventional antitetanus therapy which included antitetanus serum, sedatives, antibiotics and muscle relaxant etc." (p 25). Participants allocated to the control arm received conventional antitetanus therapy but the administration of placebo is not mentioned. No baseline data, except for the age ranges, are presented for the two trial arms. There is no description of how tetanus was diagnosed. The authors present results for 117 patients in a table indicating that all recruited patients were included in the analysis. The trialists did not state the duration of intervention or their duration of follow-up, but stated that "patients succumbed to tetanus even three to four weeks after admission" (p 27).

Thus, the Jahan 1984 trial had two age groups with treatment and control arms of similar size and administration of vitamin C

was the only systematic difference between them. However, the methodological description in the Jahan report is minimal. The role of the methodological shortcomings in the interpretation of the study results are considered in the 'Discussion' section.

We were able to contact the first author of the Jahan 1984 trial. To our query about the methods of the 1984 trial, we received this reply: "we selected two wards side by side. Patients of one ward were under treatment with vitamin C in addition to conventional treatments. In another ward patients were enrolled as a control group and got only the conventional treatment (without vitamin C). Age groups and the number of patients we tried to match as far as possible. Because we had to take the patients who were inpatients in the hospital we did not use a placebo. We were not able to hide the allocations from the physicians at that stage. Follow up of the patients was until they were discharged as fit persons or died. Diagnosis of the disease was done by a physician specialised in infectious diseases" (Professor Khursheed Jahan, 9 July 2007; personal letter).

Effects of interventions

Preventing tetanus

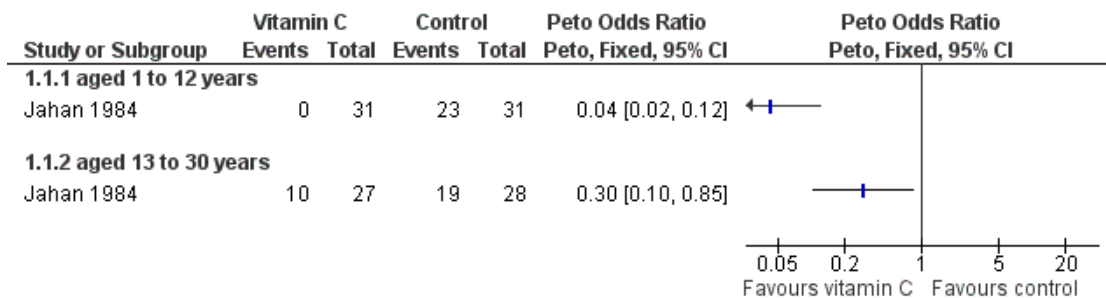
We did not identify any trials describing the effects of vitamin C as a prevention for tetanus.

Treating tetanus

Effect on case fatality rate

We identified one controlled trial that examined the effects of 1 g/day vitamin C given intravenously for tetanus patients (Jahan 1984). At recruitment, the tetanus patients were stratified into two age groups and the results were reported by the age groups. Since one of the 2×2 table cells was empty among the younger patients, in Figure 1 we present the effect estimates for OR by using the Peto-method.

Figure 1. Effect of vitamin C on tetanus case fatality rate by age groups in Jahan 1984



Age group 1 to 12 years: vitamin C significantly reduced the case fatality rate (0%; 0/31) compared with the control group (74%; 23/31). The Peto-OR for the difference between the vitamin C and control groups was 0.04 (95% CI from 0.02 to 0.12); this is shown as subgroup 1 in [Figure 1](#). Because of the empty cell, we also calculated the exact 95% CI for the OR for the young tetanus patients. The exact OR of death was 0.0 (95% CI from 0.0 to 0.06) which is thus slightly narrower than the 95% CI of the Peto-OR ([Figure 1](#)). The Fisher's exact test gives $P = 10^{-9}$ for the comparison of vitamin C and control arms of the young patients.

Age group 13 to 30 years: vitamin C significantly reduced the case fatality rate (37%; 10/27) compared with the control group (68%; 19/28). The Peto-OR for the difference between the groups was 0.30 (95% CI from 0.10 to 0.85); this is shown as subgroup 2 in [Figure 1](#). The inverse variance RR estimate given by RevMan is $RR = 0.55$ (95% CI: 0.31 to 0.95; $P = 0.03$), which is a more practical measure of vitamin C effect than the OR.

Heterogeneity between the subgroups

We found strong evidence of heterogeneity in the effect of vitamin C between the young and old patients with $P = 0.01$ for the test of heterogeneity over the two age groups. The I^2 value of 85% indicates a high level of heterogeneity. The authors of the [Jahan 1984](#) trial reported the results of the age groups separately. We did not calculate a pooled vitamin C effect because of the high level of heterogeneity.

Sensitivity analysis based on the rejection of trials with lower methodological quality was not possible because we identified only one trial.

DISCUSSION

Quality of the evidence

We identified one trial that examined the therapeutic effect of vitamin C on the mortality of people with tetanus ([Jahan 1984](#)). In this 2013 update, no new trials were identified. The [Jahan 1984](#) trial reported a highly significant benefit associated with intravenous vitamin C on the case fatality rate of tetanus patients. The methods used in the Jahan trial were, however, unsatisfactory and superficially described. Here we will consider whether potential biases could explain the differences reported in the case fatality rate between the vitamin C and control arms.

[Jahan 1984](#) did not state an explicit case definition for tetanus. Although this is a shortcoming in the report, it does not seem reasonable to assume that tetanus was improperly diagnosed in an infectious diseases hospital in a country that had a high incidence of this disease (currently the incidence is lower). Furthermore, the trial author described in a personal letter that the diagnosis was by a "physician specialised in infectious diseases".

Selection bias operates when there are systematic differences between comparison groups at baseline. Adequate randomisation with allocation concealment guards against it. No data were presented by [Jahan 1984](#) to allow us to judge whether the allocation process resulted in balanced allocation between treatment groups for prognostic factors. This trial was not randomised and there is a risk of selection bias (the ward a patient was allocated to determined whether they received vitamin C, and there might have been a systematic difference in the allocation to the wards). However, it is highly unlikely that potential baseline differences could lead to such great difference in mortality between the study arms as reported for the younger patients.

Performance bias operates when there are systematic differences in the care provided apart from the intervention being evaluated. [Jahan 1984](#) stated that both vitamin C and control arms received "conventional antitetanus therapy which included antitetanus serum, sedatives, antibiotics and muscle relaxant etc.", so the administration of vitamin C was the only systematic difference between the trial arms. However, the vitamin C and control patients were treated in different wards, which is unsatisfactory because aspects of treatment could be somewhat different between

the two wards. Placebo was not used in Jahan 1984, however, a recent meta-analysis showed that, in trials examining various topics, placebo arms did not differ from no-treatment arms if the outcome was binary; e.g. mortality (Hrobjartsson 2010). Thus, the care providers may have been aware of which arm the patients had been enrolled into, but it is highly unlikely that such knowledge would have altered treatment to such an extent that it could explain the difference in mortality between the study arms as reported for the younger patients in Jahan 1984.

Attrition bias operates when there are large numbers of people who withdraw from the study or when the rates of withdrawal are different between treatment arms. Attrition bias is unlikely in Jahan 1984, since all patients allocated were followed up and analysed. Furthermore, in a personal letter, the trial author confirmed that all patients were followed up “until they were discharged as fit persons or died”.

Detection bias operates when there are systematic differences in the ways outcomes were assessed between treatment groups and is more likely to occur when there is no blinded outcome assessment and when the outcome is subjective. It is unlikely, however, that detection bias is operating in Jahan 1984 since the outcome was mortality which is not a subjective outcome. There is minimal possibility of bias in detecting mortality in a hospital.

Consequently, although the methods of the Jahan 1984 trial are poorly described and the trial was poorly conducted, the biases discussed above cannot explain the reported findings. There seems to be no basis to assume attrition bias or detection bias in the trial. Possibly there has been selection bias and performance bias to some degree, but this cannot explain the reported difference in outcomes among the younger participants. Glasziou 2007 argued that rate ratios beyond 10 are highly likely to reflect real treatment effects, even if confounding factors may contribute to the size of the observed effect. In the younger patients of the Jahan trial, the entire 95% CI and not just the point estimate is beyond the ratio of 10. In the older patients of the Jahan trial, the upper limit of the 95% CI is close to the control group level, and therefore the results are not robust to the possibility of selection and performance biases. Nevertheless, the findings in the older patients are consistent with the findings in the younger patients.

Finally, the existence of a single positive study might be explained by **publication bias**, meaning that researchers tend to report studies with ‘positive’ results but not those with ‘negative’ results. With this reasoning, it is possible that Jahan 1984 was published just because vitamin C appeared beneficial (but simply by chance), whereas several trials might remain unpublished because of their negative results. Publication bias may explain findings that are close to statistical significance, but it is not a reasonable explanation for highly statistically significant findings such as those of the younger patients in the Jahan 1984 trial. Furthermore, it would seem incomprehensible that publication bias would generate the highly significant heterogeneity over the age groups. Therefore we do not consider that publication bias is relevant in this case.

Applicability of the evidence

The Jahan 1984 trial is methodologically unsatisfactory and caution is required in the interpretation of the results. There are no other trials with humans giving independent direct support to the findings. Nevertheless, in western countries tetanus patients are treated in ICUs, and four randomised trials with critically ill patients found that vitamin C alone or with vitamin E reduced the duration of mechanical ventilation or the length of ICU stay or both (Tanaka 2000; Nathens 2002; Papoulidis 2011; Bjorndahl 2012).

In the Jahan 1984 trial, vitamin C was used over and above treatments that are still used for treating tetanus patients. In this respect, the trial is not outdated.

When considering extrapolation of the findings of vitamin C trials, one issue of particular importance is the level of dietary vitamin C intake. A different outcome between the vitamin C and control arms may result from a particularly low dietary intake in the control arm (‘marginal vitamin C deficiency’) or from the high dose supplementation in the vitamin C arm. In the former case, a small dosage of supplement may produce a similar effect, whereas in the latter case the high dose is necessary. As reference levels: scurvy may be caused by vitamin C intake of less than 10 mg/day, whereas the mean vitamin C intake, for example, in the USA is about 100 mg/day (IOM 2000).

If the biological basis for the results in Jahan 1984 was the treatment of marginal deficiency, this would not provide an explanation for the significant heterogeneity between the age groups, as the dose is so high that it would cure marginal deficiency in both age groups. Thus, it is possible that the high dose, 1 g/day, was essential for the results. The benefit of vitamin C was significantly greater for the younger patients (1 to 12 years), who weigh on average less than the older patients (13 to 30 years). Thus the heterogeneity might have resulted from dose dependency because the dose per weight was higher in the younger patients. However, there are other differences between the younger and older patients, and some of them might explain the heterogeneity as well.

In the Jahan 1984 trial, vitamin C was administered intravenously which increases plasma level substantially more than oral administration (Padayatty 2004). Therefore, the same dose of vitamin C as tablets might not have similar effects.

Safety of vitamin C

In the Jahan 1984 report, no adverse effects related to the intravenous 1 g/day vitamin C administration were mentioned.

Two large-scale trials with 8171 female health professionals and 14,641 male physicians found no adverse effects of 0.5 g/day of vitamin C when administered for 8 to 9 years indicating long term safety of such a dosage level (Cook 2007; Sesso 2008).

There is also evidence that high dose vitamin C is usually safe when administered intravenously. A matched case control study of cancer patients found that 10 g/day vitamin C by intravenous

infusion for 10 days and orally thereafter was associated with a longer survival time which indicates the absence of harmful effects with such a dosage (Cameron 1976). Large doses of vitamin C have been administered intravenously for numerous patients without adverse effects (Padayatty 2006; Padayatty 2010). In a pharmacokinetic study, no adverse effects were reported with the administration of up to 100 g of vitamin C intravenously to healthy people (Padayatty 2004). A case report described the use of intravenous vitamin C doses at levels up to 28 g/day for a six-year-old boy with tetanus (Klenner 1954).

Cathcart 1981 stated that patients with severe infections can take over 30 g/day of vitamin C orally without suffering from diarrhoea, whereas healthy people can take only 4 to 10 g/day. This difference in tolerable doses may be caused by the changes in vitamin C metabolism because of severe infections (Chakrabarti 1955; Hemilä 2006). Thus, it is possible that the range of safe doses extends to higher levels in people who have severe infections compared with healthy people.

There are few reports of severe harm caused by high-dose vitamin C administration. Furthermore, the death of a 68-year-old African American man was not attributed to the intravenous injection of 80 grams of vitamin C on two consecutive days *per se*, but to his coincident glucose-6-phosphate dehydrogenase deficiency (G6PD) (Campbell 1975). Such unfortunate events do not have public health importance, although they discourage use of large vitamin C doses to G6PD patients.

Consequently, there seems to be no concern about the safety of the intravenous dosage level, 1 g/day, used in Jahan 1984.

AUTHORS' CONCLUSIONS

Implications for practice

A single poor quality and poorly reported controlled trial found that 1 g/day intravenous vitamin C significantly reduced tetanus case fatality rate. Potential biases do not easily explain the differences between the vitamin C and control groups, but the shortcomings of this trial mean that routine vitamin C use cannot be recommended on the basis of this trial alone. There were no evaluations of vitamin C as a prevention for tetanus.

Implications for research

Treatment trials: the particularly dramatic effect reported for children in Jahan 1984 implies that more research is needed into the effect of vitamin C on mortality of tetanus patients. Vitamin C should be studied as an addition to conventional therapy.

Prevention trials: because of vaccination, tetanus is nearly non-existent in children and middle-aged people in the developed world. Although vaccination should be a priority in developing countries, the prophylactic effects of vitamin C supplementation might be investigated in populations with a high incidence of tetanus and low dietary vitamin C intake levels, which coexist, for example, in Somalia (WHO 1999; WHO 2000).

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We are grateful to Sally Bell-Syer, Duncan Chambers, Nicky Cul-lum, Ruth Foxlee, Andrew Jull, Andrea Nelson, Louise Thwaites, Gill Worthy and Amy Zelman for their comments on improving the draft review, and for Margaret Carver for copy editing the review. Thanks to Helena Mullineaux who copy edited the updated review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Jahan 1984

Methods	Non randomised; allocation method not described. Vitamin C and control participants treated in separate wards. No placebo; no blinding. Duration up to 4 weeks.
Participants	117 tetanus patients admitted to the Infectious Disease Hospital, Dhaka, Bangladesh. Age group 1 to 12 years: 31 vitamin C, 31 control. Age group 13 to 30 years: 27 vitamin C, 28 control.
Interventions	Vitamin C intravenously 1 g/day vs. no vitamin C. Both groups received standard treatment
Outcomes	Case fatality rate.
Notes	Poorly described trial (see Risk of bias in included studies). Additional information was received from the first author, Professor Jahan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"we selected two wards side by side. Patients of one ward were under treatment with vitamin C in addition to conventional treatments. In another ward patients were enrolled as a control group and got only the conventional treatment (without vitamin C)". Personal communication with trial author. No randomisation took place
Allocation concealment (selection bias)	High risk	Allocation method not described, see above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients in one ward were administered vitamin C and patients in another ward served as control. This was known to personnel but it is not clear whether it was known to the patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mortality in a hospital is not biased by subjective observations

Jahan 1984 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs according to the report
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DATA AND ANALYSES

Comparison 1. Vitamin C vs control

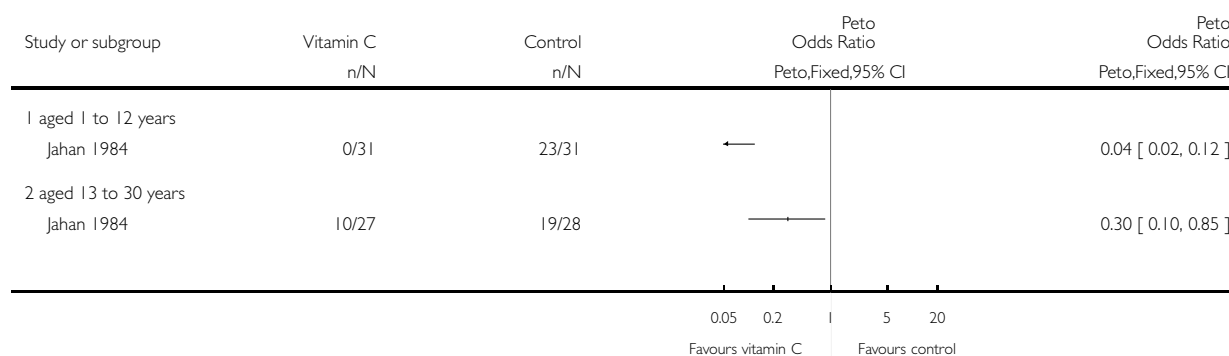
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Case fatality rate	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.1 aged 1 to 12 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 aged 13 to 30 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Vitamin C vs control, Outcome 1 Case fatality rate.

Review: Vitamin C for preventing and treating tetanus

Comparison: 1 Vitamin C vs control

Outcome: 1 Case fatality rate



APPENDICES

Appendix 1. Search methods for the second review update (2011)

Electronic searches

For an outline of the search methods used in first update of this review see [Appendix 1](#).

For this second update the following databases and dates are covered:

- Cochrane Wounds Group Specialised Register (searched 4 August 2011);
- Cochrane Infectious Diseases Group Specialised Register (searched 24 August 2011);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3);
- Ovid MEDLINE (1950 to August Week 2 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations August 18, 2011);
- Ovid EMBASE (2009 to 2010 Week 50)

The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):

#1 MeSH descriptor Tetanus explode all trees

#2 tetanus

#3 (#1 OR #2)

#4 MeSH descriptor Ascorbic Acid explode all trees

#5 ascorb* or "vitamin C"

#6 (#4 OR #5)

#7 (#3 AND #6)

The search strategies for Ovid MEDLINE and Ovid EMBASE can be found in [Appendix 2](#) and [Appendix 3](#) respectively. No methodological filters were used. No date or language restrictions were applied.

Searching other resources

Previously, [Briggs 1984](#) carried out extensive literature searches and published a bibliography containing over 400 references to papers related to vitamin C and infections, which we checked. We also searched the reference lists of all other pertinent reviews and of the potentially eligible studies identified in our search.

Appendix 2. Ovid MEDLINE search strategy

1 exp Tetanus/

2 exp Tetanus Toxin/

3 exp Tetanus Toxoid/

4 tetanus.mp.

5 or/1-4

6 exp Ascorbic Acid/

7 ascorb\$.mp.

8 (vitamin\$ adj5 C).mp.

9 or/6-8

10 5 and 9

Appendix 3. Ovid EMBASE search strategy

1 exp Tetanus/
2 exp Tetanus Toxin/
3 exp Tetanus Toxoid/
4 tetanus.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 ascorb\$.mp.
8 (vitamin\$ adj5 C).mp.
9 or/6-8
10 5 and 9

WHAT'S NEW

Last assessed as up-to-date: 16 June 2013.

Date	Event	Description
5 September 2013	New citation required but conclusions have not changed	Third update, new search, no new trials identified. No change to conclusions
5 September 2013	New search has been performed	Text updated, change from the estimation of vitamin C effect from the Mantel-Haenszel RR to the Peto OR

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

Date	Event	Description
26 August 2011	New search has been performed	Second update, new search, no new trials identified, conclusions not changed
19 November 2009	New search has been performed	New search, no new trials identified, conclusions not changed
11 November 2008	Amended	Contact details updated
6 August 2008	Amended	Converted to new review format
15 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HH wrote the draft of the protocol and TK commented on the draft. HH carried out the literature searches. Both authors assessed the search results to identify potentially relevant articles and extracted data from the articles selected. HH carried out the statistical analysis and wrote the draft of the review and TK commented on the draft. HH updated the review and TK commented the updated version.

DECLARATIONS OF INTEREST

No conflicts of interest for Harri Hemilä and Teija Koivula.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR/Department of Health (England), (Cochrane Wounds Group), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the previous versions of the review, the Mantel-Haenszel method (M-H) was used to calculate the RR as an estimate of the vitamin C effect. However, since one of the cells in the 2×2 table for the younger tetanus patients was empty, the M-H method gives substantially conservative estimates, which means much too wide 95% CI. Therefore the Peto-method was used in the 2013 update for calculating the OR as an approximation of the RR. For the young tetanus patients (1 to 12 yr), the 95% CI limits of the Peto-OR are much closer to the exact OR limits, and the P-value given by the Peto-method to the young tetanus patients ($P = 9.9 \times 10^{-10}$, $Z = 6.0$) is close to the Fisher's exact test ($P = 2.6 \times 10^{-10}$). This change does not influence the conclusions but makes the presentation in [Figure 1](#) more appropriate.

NOTES

Links to full text papers cited in this review are available at: www.mv.helsinki.fi/home/hemila/CT

INDEX TERMS

Medical Subject Headings (MeSH)

Ascorbic Acid [*therapeutic use]; Bangladesh; Tetanus [*drug therapy; mortality]; Vitamins [*therapeutic use]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant